PATENT SPECIFICATION (11) 1 577 725

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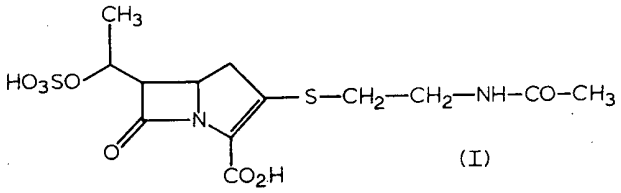
(19)

(54) AZETIDINONE DERIVATIVES

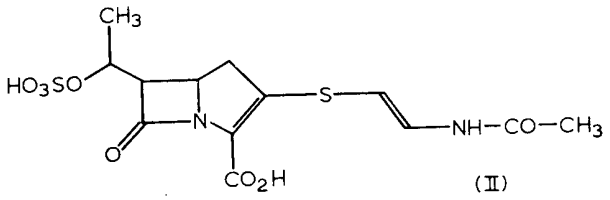
(71) We, BEECHAM GROUP LIMITED, a British Company, of Beecham House, Great West Road, Brentford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to antibacterial agents, to their preparation and to compositions containing them.

British Patent specifications Nos. 1489235 and 1483142 (see also Belgian Patents Nos. 839324 and 827332) relate to antibacterial and synergistic agents of the formulae (I) and (II).



(I)



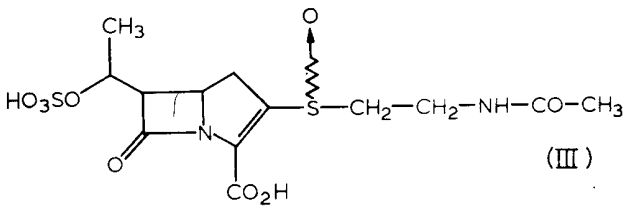
(II)

British Patent specification No. 1467413 discloses an optically pure S-oxide of the compound of the formula (II). In specification No. 1467413 that optically pure compound was designated MM 4550.

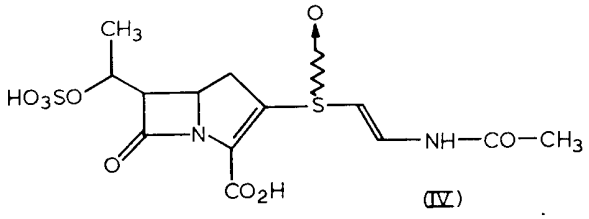
The compounds of the formulae (I) and (II) have been designated MM 17880 and MM 13902.

It has now been discovered that oxidation of the sulphide radical in these molecules leads to the preparation of novel antibacterial and synergistic agents.

Accordingly the present invention provides the compounds of the formulae (III) and (IV):



(III)



(IV)

and salts thereof said compounds being in the form of a mixture of stereoisomeric S-oxides.

Most suitably the compounds of the formulae (III) and (IV) are in the form of a mono- or di-basic salt formed with a pharmaceutically acceptable metal ion.

Preferably the compounds of the formulae (III) and (IV) are in the form of a di-alkali metal salt such as the di-sodium or di-potassium salt.

This invention also provides pharmaceutical compositions which comprise a compound of the formula (III) or (IV) or a salt thereof together with a pharmaceutically acceptable carrier.

The forms of the compositions of this invention will normally be similar to those described in the aforementioned British and Belgian Patent specifications.

Suitably the composition of this invention also comprises a penicillin or cephalosporin. Such synergistic compositions will normally contain 1 part (by weight) of penicillin or cephalosporin per $^1/_{10}$ to 10 parts (by weight) of a compound of the formula (III) or (IV) or salt thereof.

The present invention also provides a process for the preparation of the compound of the formula (III) or (IV), or a salt thereof which process comprises the S-oxidation of a corresponding compound of the formula (I) or (II) or a salt thereof.

The process of this invention is normally carried out in aqueous solution at a non-extreme temperature. Suitable temperatures include the range 0—30°C and preferred temperatures are found within the range 10—25°C.

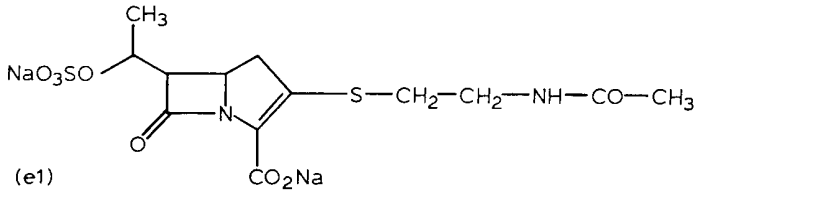
Suitable oxidizing agents for use in this process are mild oxidizing agents such as organic per acids. Particularly suitable oxidizing agents include optionally substituted perbenzoic acid, for example *m*-chloroperbenzoic acid.

Most suitably the oxidation reaction is carried out on a salt of a compound of the formula (I) or (II), for example a di-basic salt such as the di-sodium salt.

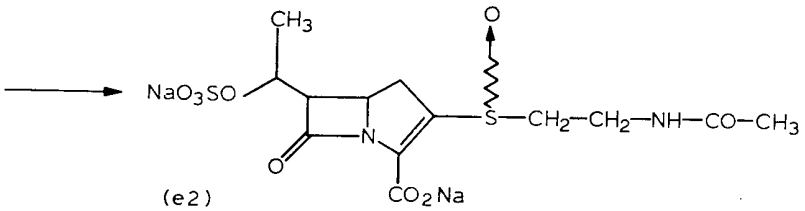
The salts of the compound of the formulae (II) and (IV) are normally isolated from an approximately neutral solution after oxidation is complete.

The following Examples illustrate the invention:

Example 1.



(e1)



(e2)

The compound (e1) (54 mg) and *m*-chloroperbenzoic acid (23.4 mg) were stirred together in water (2 ml). After 10 minutes the *m*-chlorobenzoic acid that had formed was filtered off, the pH was adjusted to 7 by the addition of a small amount

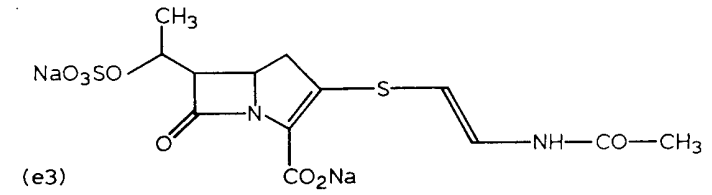
of dilute sodium bicarbonate solution and the water was then removed by evaporation on a rotary evaporator to yield the racemic mixture of compounds (e2) as a solid (60%).

ν_{max} (KBr) 1765, 1610 (broad), 1250 cm^{-1};

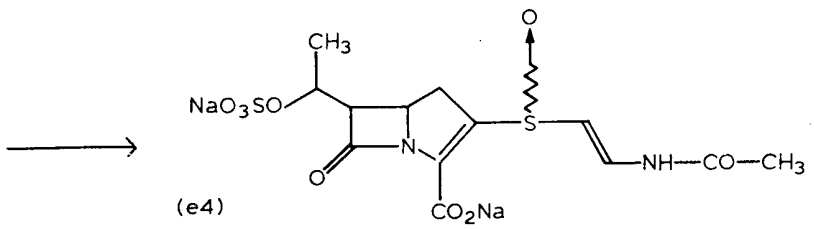
λ_{max} (H_2O) 284 nm;

δ (D_2O) 1.5 (3H, d, J = 6Hz), 2.0 (3H, s), 2.8—4.0 (m) ppm.

Example 2.



(e3)



(e4)

A solution of (e3) (0.3 g) in water (10 ml) was treated with solid *m*-chloroperbenzoic acid (0.17 g). A white precipitate of *m*-chlorobenzoic acid was rapidly formed, and after 10 minutes was filtered off. The remaining solution was neutralised to pH 7 with sodium bicarbonate and then chromatographed on QAE Sephadex A 25, eluting with NaCl — phosphate buffer ("Sephadex" is a Registered Trade Mark). The product was desalted on Amberlite XAD—4 ("Amberlite is a Registered Trade Mark) using distilled water to elute, and then freeze-dried to afford a mixture of epimeric sulphoxides (1.2:1) (e4) as a white solid (0.176 g, 57%).

ν_{max} (KBr) 1765, 1690, 1620 br, 1210—1270 br cm^{-1};

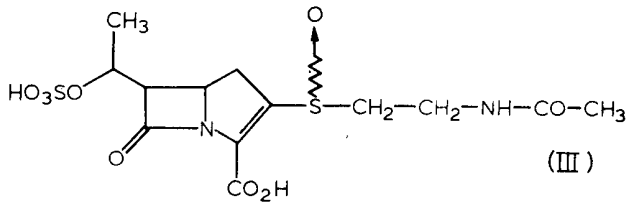
λ_{max} (H_2O) 287 and 237 nm;

δ (D_2O) 1.44 (3H, d, J = 6Hz), 2.02 (3H, s), 2.80—3.55 (2H, m), 3.85 (1H, m), 4.40 (1H, m), 4.80 (1H, m), 6.20 and 6.25 (total 1H, each d, J = 14Hz) and 7.45 (1H, d, J 14Hz).

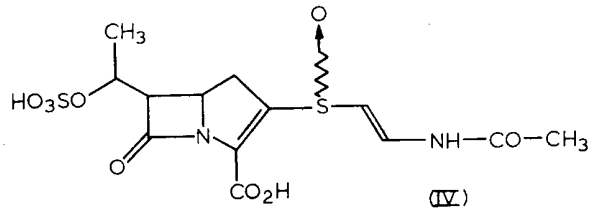
[The resonances at 6.20 and 6.25 indicate that the product is a mixture of 2 isomers and thus distinguish it from the compounds disclosed in Belgian Patent No. 827331].

WHAT WE CLAIM IS:—

1. A compound of the formulae (III) or (IV):



(III)



(IV)

or a salt thereof, said compound being in the form of a mixture of stereoisomeric S-oxides.

2. A di-basic salt formed with a pharmaceutically acceptable metal ion as claimed in claim 1.

3. A di-alkali metal salt as claimed in claim 2.

4. The di-sodium salt of the compound of the formula (III) as claimed in claim 1.

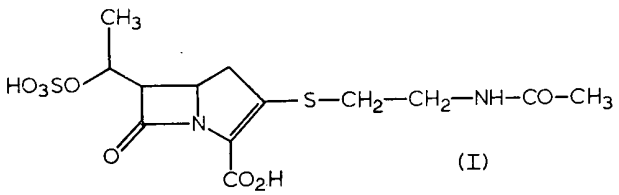
5. The di-sodium salt of the compound of the formula (IV) as claimed in claim 1.

6. A pharmaceutical composition which comprises a compound as claimed in any of claims 1—5 and a pharmaceutically acceptable carrier.

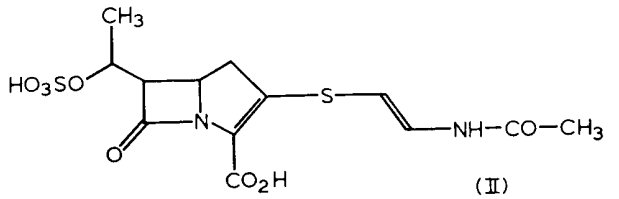
7. A composition as claimed in claim 6 which comprises a compound as claimed in any of claims 2, 3 or 4.

8. A composition as claimed in claims 6 or 7 which also comprises a penicillin or cephalosporin.

9. A process for the preparation of a compound as claimed in claim 1 which comprises the S-oxidation of a corresponding compound of the formula (I) or (II):



(I)



(II)

or a salt thereof.

10. A process as claimed in claim 9 wherein the oxidation is affected by means of an organic per acid.

11. A process as claimed in claim 10 wherein the per acid is perbenzoic or *m*-chloropherbenzoic acid.

12. A process as claimed in any of claims 9—11 wherein the compound which is oxidized is a di-basic salt of a compound of the formula (I) or (II).

13. A process is claimed in claim 12 wherein the di-basic salt is the di-sodium salt.

14. A compound as claimed in any of claims 1—5 when prepared by a process as claimed in any of claims 9—13.

15. A process for the preparation of a compound as claimed in any of claims 1—5 substantially as described in any Example herein.

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Agent for the Applicants.

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